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# Radiotheranostics: new lease of life of personalized medicine

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Radiotheranostics is a radionuclide therapy intended to perform molecular imaging *in vivo* (single-photon emission computed tomography [SPECT], positron emission tomography [PET]) using various radiopharmaceuticals (RP) and selectively affects pathological metabolic processes caused by a tumor. Thyrotoxicosis and thyroid cancer have been treated successfully using the theranostics paradigm since the 1950s with the use of radioactive iodine. In recent years, owing to advances in the development of nuclear medicine (an increase in the number of cyclotrons, SPECT/CT and PET/CT in medical institutions) and ultimately RP, radiotheranostics is developing very rapidly worldwide. The emergence of new radioligands based on  $^{177}\text{Lu}$ ,  $^{225}\text{Ac}$ , and other radioisotopes triggered a great number (>300) of clinical studies on radioligand therapy for prostate cancer, neuroendocrine tumors, pancreatic cancer, and other malignant neoplasms. One of the most promising fields of radiotheranostics application is the development of radioligands based on targeted anticancer drugs, which helps summarize two effects in one RP, namely, inhibition of the signaling cascades and radiation damage. Radiotheranostics is multidisciplinary in nature, technologically complex, and a priori integral (e.g., isotopes, RPs, SPECT, and PET), and requires high competence and teamwork. The development of radiotheranostics and elaboration of targeted RP are still at their infancy in Russia. The main problems are the lack of specialists in this field, such as doctors, physicists, chemists, radiopharmacists, biologists, geneticists, engineers, and programmers. The low awareness of doctors and patients about the possibilities of radiotheranostics also hinders its development and implementation in clinical practice in the country.

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## Радиотераностика: новое дыхание персонализированной медицины

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Радиотераностика — радионуклидная терапия, позволяющая с помощью различных радиофармпрепаратов (РФП), проводить молекулярную визуализацию *in vivo* (однофотонная эмиссионная компьютерная томография, позитронно-эмиссионная томография) и селективно воздействовать на патологические метаболические процессы, вызванные опухолью. Используя парадигму тераностики, с 1950-х годов прошлого столетия с помощью радиоактивного йода успешно лечатся тиреотоксикоз и рак щитовидной железы. В последние годы, благодаря успехам в развитии ядерной медицины (рост числа циклотронов, однофотонная эмиссионная компьютерная томография/компьютерная томография и позитронно-эмиссионная томография/компьютерная томография в медицинских учреждениях), и прежде всего радиофармацевтики, в мире очень бурно развивается радиотераностика. Появление новых радиолигандов на основе  $^{177}\text{Lu}$ ,  $^{225}\text{Ac}$  и других радиоизотопов стимулировало большое количество (более 300) клинических исследований по радиолигандной терапии рака простаты, нейроэндокринных опухолей, рака поджелудочной железы и других злокачественных новообразований. Одним из самых перспективных направлений радиотераностики является разработка радиолигандов на основе таргетных противоопухолевых препаратов, что позволяет суммировать в одном РФП два эффекта — ингибирование сигнальных каскадов и лучевое повреждение. Радиотераностика по природе своей мультидисциплинарна, технологически сложна, априори интегральна (изотопы, радиофармсубстанции, РФП, однофотонная эмиссионная компьютерная томография, позитронно-эмиссионная томография), требует высокой компетенции и командной работы. Развитие радиотераностики и разработка таргетных радиофармпрепаратов в нашей стране находится в зачаточном состоянии. Главной проблемой является нехватка специалистов в данной области — врачей, физиков, химиков, радиофармацевтов, биологов, генетиков, инженеров, программистов. Низкая информированность врачей и пациентов о возможностях радиотераностики также тормозит её развитие и внедрение в клиническую практику в нашей стране.

**Ключевые слова:** радиотераностика; радиофармацевтика; онкология.

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# 放射性核素诊疗一体化：一种新的个性化医学

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放射性核素诊疗一体化允许使用各种放射性药物在体内进行分子成像（单光子发射计算机断层摄影术，正电子发射断层摄影术），并选择性地影响肿瘤引起的病理代谢过程的放射性核素治疗。自上世纪50年代以来，利用治疗诊断学的范式，在放射性碘的帮助下，成功地治疗了甲状腺毒症和甲状腺癌。近年来，由于核医学（在医疗机构回旋加速器、单光子发射计算机断层扫描/计算机断层扫描、正电子发射断层摄影术/计算机断层摄影术数量的增加）特别是放射药物的成功发展，放射性核素诊疗一体化在世界上发展非常迅速。基于 $^{177}\text{Lu}$ 、 $^{225}\text{Ac}$ 等放射性同位素的新型放射性配体的出现，刺激了大量（超过300）的前列腺癌、神经内分泌肿瘤、胰腺癌等恶性肿瘤的放射配体治疗的临床研究。基于靶向抗肿瘤药物的放射配体的开发是放射性核素诊疗一体化中最有前途的领域之一，这使得总结出一种放射药物的两种作用—信号级联抑制和辐射损伤。放射性核素诊疗一体化本质是多学科的、技术复杂的（同位素，放射性药物，单光子发射计算机断层扫描，正电子发射断层扫描）、整体的，并要求高能力和团队合作。放射性核素诊疗一体化和靶向放射药物的发展在俄罗斯尚处于起步阶段。主要的问题是领域缺乏专家：医生、物理学家、化学家、放射性药物学家、生物学家、遗传学家、工程师、程序员。医生和患者对放射性核素诊疗一体化可能性的认识不足也阻碍了其在俄罗斯临床应用的发展。

**关键词：**放射性核素诊疗一体化；放射药剂学；肿瘤学。

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## BACKGROUND

Anticancer drug therapy is based on the shutdown of proteins in the cells of malignant tumors, which stimulate pathologically their autonomous growth, mitosis, and migration (metastasis). Immunotherapy mobilizes the body's own immunity to fight cancer. At the same time, traditional methods of treatment, such as surgery, chemotherapy, and radiation therapy, remain the mainstay of treatment for most types of cancer.

Radiation therapy was first used to treat cancer over one century ago. Today, about half of patients with cancer receive it in various forms. Until recently, most of the methods of radiation therapy were based on the remote delivery of a dose of radiation to destroy the tumor focus; however, radiation therapy is neither systemic nor selective of tumor cells. Despite its efficiency, external beam radiation therapy has many side effects associated with irradiation of healthy tissues surrounding the tumor. Even with the use of the most advanced external beam radiation therapy equipment, normal tissues surrounding the tumor are inadvertently damaged. At the same time, external beam radiation therapy and sealed-source radiotherapy, focusing mainly on the methods of structural imaging (such as endoscopy, ultrasonography, X-ray diagnostics, including mammography, multispiral computed tomography, and magnetic resonance imaging), cannot have a systemic antitumor effect by affecting local tumor foci.

A new class of drugs for "metabolic" diagnostics and treatment of tumors, called radiopharmaceuticals (RPs), is being actively developed in other countries. In radionuclide therapy, "smart" RPs are able to deliver the required dose of radiation directly to the cancer cells that have impaired metabolism. The number of clinical trials of new RPs, both diagnostic and therapeutic, is growing rapidly. These studies show that the selective delivery of radioactive isotopes to all tumor cells will improve fundamentally the diagnostics and treatment of cancers, which tend to grow and disseminate throughout the body. This type of treatment is called radionuclide therapy, and it is based on a pathologically high uptake of various metabolites by tumor cells, namely, minerals (i.e., iodine and calcium), hormone precursors, other biologically active substances (e.g., norepinephrine and dopamine), hormone receptors that are overexpressed on the surface of tumor cells (such as somatostatin, prostate-specific antigen, and glucagon-like peptide), and monoclonal antibodies (e.g., CD20 and CD38).

A huge number of new RPs, especially for therapeutic purposes, is currently studied in various phases of clinical trials. These are diagnostic RPs based on SPECT (such as  $^{99m}\text{Tc}$  and  $^{123}\text{I}$ ) and PET isotopes (i.e.,  $^{13}\text{N}$ ,  $^{11}\text{C}$ ,  $^{15}\text{O}$ ,  $^{18}\text{F}$ ,  $^{67}\text{Cu}$ ,  $^{68}\text{Ga}$ ,  $^{82}\text{Rb}$ , and  $^{89}\text{Zr}$ ). Radioisotope diagnostics of pathological foci by replacing the diagnostic isotope in the RP with a therapeutic one (e.g.,  $^{131}\text{I}$ ,  $^{177}\text{Lu}$ ,  $^{90}\text{Y}$ ,  $^{223}\text{Ra}$ , and  $^{225}\text{Ac}$ ) reveals the possibilities for systemic radioligand therapy, or

radiotheranostics. This new strategic algorithm has been rapidly developing worldwide.

In the near future, radiotheranostics will expand the horizons of endocrinology, oncology, cardiology, neurology, and other fields of medicine.

## FUNDAMENTAL METABOLISM

Delivering radiation directly to tumor cells is not a new approach in medicine. Radioactive iodine therapy has been used since the 1940s to treat thyroid cancer and thyrotoxicosis. Iodine is naturally actively captured and accumulated not only in normal cells of the thyroid gland, but also in cells of a malignant tumor. As a rule, cells of differentiated thyroid cancer (~95% of all cases) retain this metabolic mechanism provided by the sodium-iodine symporter functioning. Fundamental research has revealed specific breakdowns in genes that disrupt the sodium-iodine symporter functioning, which opens up new views for planning and predicting the efficiency of radioactive iodine therapy. By contrast, this motivates us to develop new targeted drugs to influence malfunctioning metabolic processes due to genetic breakdowns in various cancer diseases.

When swallowed (as a capsule or liquid), radioactive iodine is accumulated and kills cancer cells without distinction of their location. Individual targeted biodosimetry enables calculation of more effective and safe activities of radioactive iodine for systemic therapy of tumor foci.

A similar natural metabolic mechanism was later used in the development of drugs for the treatment of cancer with bone metastases, such as radium-223 dichloride (Xofigo), approved by the Food and Drug Administration (FDA) in 2013, for the treatment of metastatic prostate cancer. Metastatic foci in the bone marrow cause destruction of bone tissue. The body then tries to repair this damage by regenerating new bone with the use of osteoblasts. This is a natural defense process that requires loads of calcium. Radium, as a chemical element, is a metabolic analog of calcium, which accumulates selectively in bone metastases and destroys them.

Researchers wondered if it was possible to create new radioactive molecules specifically for other cancer diseases. They presented engineered RPs, which are made up of three basic building blocks, namely, a radioactive molecule, a target molecule (which recognizes cancer cells and attaches to them), and a linker that connects these two elements. Such compounds, as a rule, are administered into the bloodstream, and they are selectively accumulated therefrom in the pathological foci that were previously identified during radionuclide diagnostics.

RPs work best when they can penetrate cells. Irradiation of neighboring cells creates an additional therapeutic effect, but its range is limited, so the surrounding healthy tissues will not be greatly affected. Alpha emitters have much less distance run in tissues (<0.1 mm) than beta emitters (usually

up to 2 mm). When an RP adheres or penetrates a cancer cell, the radioactive isotope decays there, releasing energy that damages the DNA of this cell and its neighboring cells. Cancer cells are susceptible to radiation-related damage to the DNA. When a cell's DNA is irreparably damaged, the cell dies.

Depending on the type of radioactive radiation used (gamma, beta, and alpha), the energy affects not only the target cell, but also 10–30 surrounding cells, which enable killing more cancer cells with one RP molecule.

By the mid-2010s, the US FDA approved two new RPs targeting specific B-cell molecules for the treatment of patients with non-Hodgkin's lymphoma, one of the hematological diseases. However, these drugs were not widely used, as physicians of patients with lymphoma were untrained and were simply apprehensive about prescription of these radioactive compounds to their patients. In addition, non-radioactive anticancer drugs are competing to the new RPs, and their manufacturers were involved in informing and training doctors.

The turning point in radiotheranostics was in 2018 when the FDA approved  $^{177}\text{Lu}$ -DOTATATE (Lutathera) RP for the treatment of neuroendocrine tumors (NETs) of the digestive tract (NETTER 1 study). Currently, clinical studies of peptide-receptor radionuclide therapy with  $^{177}\text{Lu}$ -DOTATOC are being completed and are planned with  $^{177}\text{Lu}$ -DOTANOC. These peptide radioligands adhere to somatostatin receptors activated on the surface of NETs. The wider the spectrum of radioligands, the more individualized the treatment can be, based on the results of molecular imaging, namely, single-photon emission computed tomography (SPECT) or positron emission tomography (PET), at the diagnostic stage.

In the same way, according to global leading experts, the use of RPs accumulating selectively can possibly affect other solid tumors.  $^{177}\text{Lu}$ -DOTATATE was better at inhibiting the growth of NETs (randomized controlled trial phase III NETTER-1) than any drug used previously. This was a quantum leap in the development of radiotheranostics.

## FROM VISUALIZATION TO THERAPY

Currently, researchers are developing and testing new RPs for the treatment of various cancers, such as melanoma, lung cancer, colorectal cancer, pancreatic cancer, brain cancer, multiple myeloma, and lymphoma. Any tumor that has a targeted molecule (such as receptor, transporter, and antibody) on the cell surface and good blood supply represents a potential target for radiotheranostics.

PET techniques, using short-lived radionuclides, can detect tumor foci throughout the body at once. The resolution limit of modern models of PET/CT devices is up to 2–3 mm. The higher the metabolic activity of a tumor, the higher is the chance of detecting it, even at microscopic sizes. Researchers have learned to repurpose targeted diagnostic molecules

to “charge” them with a powerful radioactive isotope to not only visualize, but also treat tumor foci.

Prostate cancer was one of the first beneficiaries of this repurposing. A protein called prostate-specific membrane antigen (PSMA) is found in high amounts and is very active in prostate cancer cells. Several RPs targeting PSMA receptor overexpression are currently studied in clinical trials.

Most prostate cancers are sensitive to radiation exposure or can be resected through traumatic surgery. However, the use of these local methods of treatment for disseminated or recurrent cases of cancer is challenging, when tumor cells spread throughout the body, forming widespread metastases in different organs. Systemic anticancer therapy is the treatment of choice in these clinical situations. The combination of antitumor drug effect and systemic tumorotropic radiation exposure constitute an ideal choice.

The administration of RPs with high tropism for PSMA receptors overexpressed on tumor cells (which is established during radionuclide diagnostics using SPECT and PET) is the best method of selective radionuclide therapy, as once in the bloodstream, RP attaches to prostate cancer cells throughout the body. The advantage of “smart” molecules for imaging and therapy (radiotheranostics), using the same metabolic target, is the fact that preliminary radionuclide imaging (i.e., SPECT and PET) provides a preliminary idea of whether treatment will give result.

In addition to the well-proven radiotheranostic ligands DOTATATE (NETs) and PSMA (prostate cancer), great expectations in oncology are associated with the new ligand fibroblast-activation-protein inhibitor. This ligand has demonstrated high and theranostic (radionuclide diagnostics + therapy) efficacy in more than 30 malignant tumors.

## PERSONALIZATION OF COMBINED CANCER THERAPY

Although RPs have shown promising results in early studies, it cannot be confirmed whether they, like other types of anticancer drugs, will destroy independently all tumor foci.

The use of RPs in combination with other treatment methods is the main paradigm for a personalized combination of potentially effective methods of treatment. Many researchers are now testing RP in combination with radiation sensitizers, drugs that make cancer cells even more vulnerable to radiation. For example, clinical trials are performed for lutetium  $^{177}\text{Lu}$ -DOTATATE in combination with the radiation sensitizer triapine, which blocks the production of compounds by cells, required for DNA repair after radiation damage. Another study is testing  $^{177}\text{Lu}$ -DOTATATE with a poly (ADP-ribose) polymerase (PARP) inhibitor. These drugs, already approved for treatment of certain types of breast, ovarian, and other cancers, block the DNA repair process itself. Thus, radiation can cause DNA damage, and a PARP

inhibitor will prevent tumor cells from healing their DNA after irradiation.

Research on combined radionuclide and immunotherapy is also being conducted to improve the efficiency of treatment without increasing its toxicity. Recent studies have shown that RPs can increase the sensitivity of tumors to immunotherapy.

Many tumors are “invisible” to immune therapy because immune cells do not recognize them or do not work properly in the microenvironment around tumors. When cancer cells are destroyed by radionuclide therapy, proteins, and DNA from those cells enter the bloodstream so that immune cells can recognize them. Radionuclide therapy helps transfer tumor foci from being invisible to being targets of immunotherapeutic drugs by even partially destroying them. Immunotherapy is proved to work better if every metastasis in every tumor is exposed to radiation, as is the case with systemic radionuclide therapy.

In the future, it is reasonable to combine RPs with external beam radiation therapy, especially for large foci and/or those partially resistant to radionuclide therapy. Dosimetric and topometric planning of such combined radiation therapy ensures an effective and safe treatment plan.

## FROM DISINTEGRATION

## TO INTEGRATION AND TEAM WORK

The development of radiotheranostics and elaboration of targeted RPs are in infancy in Russia. The main problem is the lack of specialists in this field, namely, doctors, physicists, chemists, radiopharmacists, biologists, geneticists, engineers, and programmers.

Russia has no specific field of nuclear medicine, as it exists in all other developed countries. By its nature, nuclear medicine is multidisciplinary, technologically complex, and a priori integral (isotopes, RP, SPECT, PET), and requires high competence and teamwork. At the same time, the field is rapidly developing and is being re-equipped, updated with innovative targeted RPs. Molecular imaging, dosimetry, evidence base of knowledge, information, and analytical technologies for the formation of artificial intelligence in the field of radiomics and radiogenomics are being improved. In the author's opinion, the main problem is the absence of appropriate personnel and technologies. In Russia, no relevant

educational programs, specialties, or scientific schools are established. This field is being developed very rapidly that, even in the United States, there is an acute shortage of doctors and related nuclear medicine specialists.

A serious problem is the lack of contemporary and licensed (Good Manufacturing Practice) RP production in the country of both medical radioactive isotopes and cold kits for their manufacture in medical institutions (world practice). In Russia, not a single modern therapeutic RP is being developed and is not planned to be introduced.

The low awareness of Russian doctors and patients about the possibilities of radiotheranostics also hinders its development and implementation in clinical practice.

## CONCLUSION

New RPs are surprising, and they cause mistrust and disbelief in their availability, as well as in the attitudes of doctors and patients. However, only doctors, and through their patients, are able to obtain the real benefits from the introduction of technology into the clinical practice. In recent years, the great breakthrough in radionuclide diagnostics and therapy is based on the ability to integrate technologies and competencies. This cannot be done without teamwork from planning and production, from the laboratory cabinet to the patient's bed.

In 2019, in the United States, the National Cancer Institute launched the Radiopharmaceutical Development Initiative to accelerate further trials of new promising RPs. Similar programs of state support for radiopharmacy and radiotheranostics have also been launched in Europe, Australia, etc.

We should also think over such integration programs for the development of radiopharmacy and radiotheranostics, especially taking into account existing trends and potential leadership opportunities (production of isotopes, pharmaceutical substances, development of SPECT and PET technologies, radionuclide therapy departments, and personnel training) in Russia.

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